Executive Summary

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

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Subject: Joint NDAC/DODAC Advisory Committee Meeting, May 6 – 7, 2004

Background

Tinea pedis is a dermatophyte infection of the feet. It can present in different variant forms, including chronic intertriginous (interdigital), which is the most common presentation and the form most commonly studied in clinical trials. Eleven ingredients are currently approved through new drug applications (NDAs) for prescription or over-the-counter (OTC) use for this disease. Seven ingredients were found to be generally recognized as safe and effective (GRASE) for the treatment of tinea pedis and are included in a drug monograph[1] for OTC topical antifungal drug products.

Efficacy and Safety

The basis for the approval of the drugs submitted in NDAs has been superiority of the drug product over the vehicle. In general, these products have not been rigorously tested for identification of the dose and dosing regimen that can provide an optimal benefit-risk ratio. Most efficacy studies have included only a single dosing regimen and a single concentration compared to a vehicle control. FDA (we) have asked sponsors to conduct dose-response studies to test multiple concentrations of the active ingredient and vary the daily rate and duration of product application. For the most part, this advice has not been followed.

Recently, there have been inquiries from sponsors about developing drug products with treatment durations of less than one week. During the meeting, we will present efficacy data from many of the currently marketed products. A brief synopsis is included in the background material. Given the cure rates for the current products and the direction of development programs for future products, it is important for the committee to provide advice on clinical trial designs and future development programs. The

[1] A brief description of the OTC drug review and monograph development process is included in the background material. OTC drug monographs are published in the Code of Federal Regulations.

ultimate goal is to provide products that maximize the likelihood of complete cure for the consumer.

Consumer Use and Labeling of Products

The effectiveness of the treatment of tinea pedis may not be evident for several weeks after application of the product has ceased. This is particularly true for products administered for one week. Resolution of symptoms and cure of the tinea pedis infection lags behind the application of the product. For this reason, the primary measures of efficacy in the clinical trials are assessed several weeks after therapy is stopped.

The background material includes a summary of the labeling for some of the products currently marketed. Some labels are more informative than others in conveying efficacy information (e.g. cure rates, the lag time between completion of therapy and symptom resolution). The committee will be asked to discuss the current content of labels and whether to include additional information regarding the efficacy and expectations for success. We have received reports of lack of efficacy related to the use of these products. It may be that the expectations of consumers exceed the efficacy observed in clinical trials.

Complications of Tinea Pedis

We will present information on complications associated with untreated or undertreated tinea pedis infections (e.g. secondary cellulitis) and whether drug resistance should be a concern given the complete cure rates observed in the clinical trials. The background information includes a summary of cases of cellulitis from the FDA adverse event reporting system.

Background Package

1. Natural history of tinea pedis infections
2. Study design and efficacy results for tinea pedis clinical trials
3. History and overview of the over-the-counter monograph for topical antifungal drug products
4. Final monograph for topical antifungal drug products 21 CFR 333
5. Over-the-counter drug product labeling
    a. For topical antifungal drug products
    b. For other products that convey efficacy information
6. Adverse event reports for lack of efficacy and cellulitis for products used to treat tinea pedis

Presentations

1. Natural history of tinea pedis
2. Complications associated with tinea pedis
3. Fungal resistance related to the treatment of tinea pedis
4. Efficacy study design and cure rates for products to treat tinea pedis
5. OTC drug monograph for products to treat tinea pedis

6. Comparison of efficacy rates and labeling for topical antifungal drug products marketed under NDAs and the monograph (including discussion of OTC product labeling for other therapeutic categories)

Discussion Points

- Efficacy of current products marketed for the treatment of tinea pedis
- Development programs and trial designs for tinea pedis indications
  - Dose response
  - Treatment duration
  - Endpoints
- Labeling of products to treat tinea pedis
- Fungal infection and drug resistance
- Complications related to tinea pedis (e.g. secondary cellulitis) and at risk populations